REMARKS

Claims 6, 9, 10, 12-22, 28-34, and 36-45 were pending in the application. Claims 12-16, 18-22, 37, 44, and 45 have been cancelled as being drawn to a non-elected invention. Claims 9, 10, 17, 39-43, and 46 have been amended. New claims 47-62 have been added. Accordingly, upon entry of the foregoing Amendment and Response, claims 6, 9, 10, 17, 28-34, 36, 38-43, and 46-62 will be pending in the application.

Support for the amendment to claims 39, 40, and 43 can be found in the specification, including at least in Tables I and IV, at page 12, line 15 and at page 29, lines 25-26. Support for the amendment to claim 46 and new claims 47, 50, 52, 54, 56, 58, and 59 can be found in the specification, including at least in Tables I and IV, as well as page 31, lines 29-31, page 33, lines 25-26, and page 35, lines 28-29. Support for new claims 48, 49, 51, 53, 55, 57, 59, 60, and 61 can be found in the specification, including at least in Tables I and IV. The foregoing amendments and new claims introduce no new matter and are not related to issues of patentability.

The foregoing claim amendments should in no way be construed as an acquiescence to any of the Examiner's rejections and were made *solely* to expedite prosecution of the present application. Entry of the foregoing Amendment and Response is respectfully in order and requested. Applicant reserves the right to file the claims as originally filed in this or a separate application(s), as well as file divisional applications to claims directed to non-elected invention, *e.g.*, claims 12-16, 18-22, 37, 44, and 45.

The specification has been amended to include SEQ ID NOs for the sequences described in Table 1. In addition, the pentapeptide sequences of MD820 and MD61 have been included in Table I, where each sequence has also been assigned a SEQ ID NO. Support for this amendment can be found in Tables IV, V, and VI. No new matter has been added.

Restriction Under 35 U.S.C. 121 / Objection to Claims

With respect to the Examiner's indication that the restriction of the claims, as set forth in the Restriction Requirement (dated December 14, 2006), is maintained and made final, as well as the Examiner's indication that claims 9, 10, and 41 are objected to for containing non-elected subject matter, Applicant provides the following.

Applicant notes that the Restriction Requirement indicated that the claims would be examined to the extent they read upon the elected species, and furthermore, that upon allowance of generic claim "applicant will be entitled to consideration of claims to additional species." Claim 10

depends from generic linking claim 39, and has been amended to recite the SEQ ID NOs of the full length recombinant inhibitor protein sequences corresponding to the recited reference numbers. Applicant respectfully submits that the non-elected sequences will be searched once claim 39 is indicated allowable. Applicant respectfully submits that maintenance of the subject matter of claim 10 is proper, as Applicant understands that each of the sequences of claim 10 will be searched upon an indication of the allowabilty of generic claim 39. As indicated by the Examiner, these sequences represent patentably distinct species of the same invention, *i.e.*, subjected to a species election for search purposes. Accordingly, Applicant respectfully requests that the Examiner withdraw the objection to claim 10. Should be Examiner maintain the objection, clarification is requested.

SEQ ID NOs: 16 to 22 recited in claim 41 correspond to modified RSLs (corresponding to the full length recombinant inhibitor protein sequences described in claim 10) identified by Applicant as having advantageous properties, *i.e.*, inhibiting kallikrein. Applicant notes that in the Restriction Requirement, the Examiner required Applicant to identify a species sequence from SEQ ID NOs: 16 to 22 for search purposes, *i.e.*, a species election for search purposes. As such, it is Applicant's understanding that the remainder of the species of claim 41 will be searched upon allowance of the elected species. As indicated by the Examiner, these sequences represent patentably distinct species of the same invention, *i.e.*, subjected to a species election for search purposes. Accordingly, Applicant respectfully requests that the Examiner withdraw the objection to claim 41. Should be Examiner maintain the objection, clarification is requested.

Finally, the Examiner has also requested that Applicant delete non-elected subject matter from claim 9, which recites serpin protein sequences which may be used in the recombinant inhibitor proteins of the invention. Applicant also notes that the Examiner has indicated that this election was not a species election. Applicant respectfully requests that the Examiner reconsider this position, as an allowable linking claim (claim 39) has been provided which links the serpin proteins of claim 9. As such, Applicants have not amended claim 9 at this time to delete reference to serpin proteins other than ACT, should the Examiner reconsider the position on this matter.

Objections to the Oath or Declaration

The Examiner has objected to the Declaration filed on July 25, 2006 alleging that the Declaration is defective because it "does not claim priority to PCT/IB04/01040 filed on 4/05/2004." Applicant respectfully submits that the Declaration filed on July 25, 2006 properly references PCT/IB04/01040 at page 1 of the document as the international application from which the instant 371 application derives. Moreover, MPEP 8193.03(c) states that

> a national stage application submitted under 35 U.S.C. 371 may not claim benefit of the filing date of the international application of which it is the national stage since its filing date is the date of filing of that international application. See also MPEP § 1893.03(b). Stated differently, since the international application is not an earlier application (it has the same filing date as the national stage), a benefit claim under 35 U.S.C. 120 in the national stage to the international application is inappropriate...

The Examiner is incorrect in requesting a Declaration in which the instant application claims priority to the PCT application, as the PCT application is not a priority document for the instant application. Rather, the instant application is a 371 national phase of the PCT application. PCT and 371 applications share the same filing date. The PCT application is not a prior-filed foreign application, as indicated by the Examiner. Thus, Applicant submits that the executed Declaration submitted on July 25, 2006 complies with the statutory requirements.

Rejection of claims 10, 28, and 39-43 under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 10, 28, and 39-43 under 35 U.S.C. § 112, second paragraph, for being indefinite.

Claim 10 has been rejection for reciting the phrase "MD 67." Applicant submits that in view of the teachings of the specification regarding MD67, one of ordinary skill would readily understand this term. In the interest of expediting prosecution, however, claim 10 has been amended to recite the SEQ ID NO associated with the full length MD67 protein (SEQ ID NO: 8).

Claims 28 and 39-43 have been rejected for use of any one of the phrases "specific for [a or said] kallikrein," "for said kallikrein," "specific for kallikrein hK2" and "for said kallikrein hK2." Applicant submits that in view of the teachings of the specification and the knowledge in the art, one of ordinary skill would readily understand these phrases. Claims 28 and 39-43 have been amended to recite the phrase "which inhibits" a kallikrein or hK2. In view of the amendments to claims 28 and 39-43, Applicant respectfully requests that the Examiner withdraw the rejection.

Rejection of claims 6, 9, 10, 17, 28-34, 36, 38-43, and 46 under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 6, 9, 10, 17, 28-34, 36, 38-43, and 46 under 35 U.S.C. § 112, first paragraph. The Examiner suggests that claims 6, 9, 10, 17, 28-34, 36, 38-43, and 46 fail to comply with the written description requirement, and that the claims contain subject matter which was not described in the specification in a reasonable way to convey to one of skill in the art that Applicant's were in possession of the claimed invention at the time of filing.

Applicants respectfully traverse the foregoing rejection and submit that, based on the teachings in Applicant's specification, one skilled in the art would reasonably conclude that Applicants were in possession of the claimed invention at the time the application was filed.

As amended, claim 39 is directed to a recombinant inhibitor protein, or an inhibiting fragment thereof, which inhibits a kallikrein, comprising a serpin sequence comprising a modified Reactive Serpin Loop (RSL) having a substituted P1-P1'scissile bond-containing pentapeptide, wherein P1 is an arginine (R) or a lysine (K) which results in increased binding affinity for said kallikrein. Amended claim 40 is directed to a recombinant inhibitor protein, or an inhibiting fragment thereof, which inhibits kallikrein hK2, comprising a serpin sequence comprising a modified Reactive Serpin Loop (RSL) having a substituted P1-P1'scissile bond-containing pentapeptide which results in increased binding affinity for said kallikrein hK2. Applicant notes that amended claims 39 and 40 encompass a genus which is defined by both structural, *i.e.,* a serpin sequence comprising a modified Reactive Serpin Loop (RSL) having a substituted P1-P1'scissile bond-containing pentapeptide, and functional, *i.e.,* inhibits kallikrein or hK2 and also has increased binding affinity for kallikrein or kH2, features.

Claim 41 has been amended to specify a recombinant inhibitor protein which inhibits a kallikrein, or a kallikrein inhibiting fragment thereof, comprising a serpin sequence comprising a modified Reactive Serpin Loop (RSL), wherein the amino acid sequence of the modified RSL is selected from the group consisting of SEQ ID No 16, 17, 18, 19, 20, 21, and 22. The SEQ ID NOs recited in amended claim 41 correspond to modified RSLs comprising pentapeptides identified by Applicant as having high affinity for kallikrein (see sequences described in Table IV (amended herewith to include the respective SEQ ID NOs) and inhibition profile described in Table V of the specification).

Amended claim 43 is directed to a recombinant inhibitor protein, or an inhibiting fragment thereof, which inhibits a kallikrein, comprising a serpin sequence comprising a modified Reactive Serpin Loop (RSL), wherein P6 – P6' of the RSL comprises an arginine (R) or a lysine (K) at P1 and at least one additional substrate active site sequence. Amended claim

43 requires both structural, *i.e.*, P6 – P6' of the RSL comprising an arginine (R) or a lysine (K) at P1 and at least one additional substrate active site sequence, and functional, *i.e.*, kallikrein inhibiting, features of the claimed recombinant inhibitor protein.

Thus, recombinant inhibitor proteins encompassed by the genus of amended claims 39-41 and 43 require both structural, *i.e.*, a serpin and a modified RSL comprising a pentapeptide, and functional, *i.e.*, kallikrein inhibition, features in accordance with the written description requirement. The specification teaches the relationship between the structural features of the claimed proteins and their functions. For example, Table IV describes examples of RSLs which contain pentapeptides within the P6-P6' region of the RSL, each of which confer kallikrein inhibiting properties to the serpin in which said sequences are included (see inhibition results described in Tables V and VI and Example 1).

Amended claims 39, 40, 41, and 43 are drawn to a genus of kallikrein inhibiting recombinant inhibitor proteins having modified RSLs which comprise pentapeptides that confer improved inhibition of kallikrein top the protein. Applicant respectfully submits that there is sufficient written description in Applicant's specification regarding the claimed kallikrein inhibiting recombinant inhibitor proteins to inform a skilled artisan that Applicant was in possession of the claimed invention at the time the application was filed. Applicant also respectfully submits that a representative number of species within the claimed genus is disclosed in the specification to satisfy the written description requirement. As amended, claims 39, 40, 41, and 43 require that the recombinant inhibitor protein comprise a serpin and a pentapeptide, which the specification teaches confers kallikrein inhibiting properties to the serpin protein. The specification provides numerous examples of pentapeptides that may be used in the invention (see for Example Table 1). The specification also provides working examples which describe how to make *six* different recombinant inhibitor proteins comprising serpin proteins having modified RSLs, *i.e.*, ACT comprising six variant pentapeptides (see pages 26 to 29). The specification also describes that the six ACT proteins having modified RSLs are more effective at inhibiting a kallikrein versus wild type ACT having an unmodified RSL (see Example 1, including Tables IV – VI). Not only does the specification provide working examples, but Applicant also teaches how to screen for additional pentapeptides that may be used in the recombinant inhibitor proteins of the invention, including phage display screening (see page 22, line 1 to page 23, line 14 and page 28). Applicant further teaches advantageous positions for the pentapeptides within the RSL (see, for example, Tables I and IV). Pages 23-24

and the working examples of the specification teach how to introduce the pentapeptides into the serine protease, which is essentially used as a scaffold for the pentapeptide.

With respect to the Examiner's suggestion that the working example describing ACT is not a representative number for the claimed genus, Applicants respectfully disagree. As described in MPEP 2163,

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), *or by disclosure of relevant, identifying characteristics*, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. (emphasis added)

The specification not only describes six versions of ACT having pentapeptides which inhibit kallikrein, but also provides teachings regarding additional serpins which may be used in the invention. For example, at pages 10-12 and Table II, the specification describes examples of serpins other than ACT known in the art which may be used in the recombinant inhibitor proteins of the invention. It is known in the art, as described at pages 2-3 of the specification, that serpins have similar structural features, including an RSL. Thus, Applicant submits that the specification satisfies the written description requirement by providing a representative number of species, as well as methods for identifying additional species, for each of the genera cited by the Examiner as lacking written description support.

With respect to the new claims, Applicants submit that these claims also fulfill the written description requirement set forth under 35 USC 112, first paragraph.

Accordingly, the present specification and amended claims comply with the written description requirement as set forth under 35 U.S.C. 112, first paragraph, and Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

Rejection of claims 6, 9, 10, 17, 28-34, 36, 38-43, and 46 under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 6, 9, 10, 17, 28-34, 36, 38-43, and 46 under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner suggests that the specification is enabling for ACT comprising an amino acid sequence set forth in SEQ ID NO: 8, but that the

specification fails to provide enablement for any recombinant inhibitor protein, or inhibiting fragment thereof, comprising a serpin sequence comprising a modified RSL, wherein the modified RSL is modified at any substrate active site sequence resulting in increased binding affinity for a kallikrein. Applicant respectfully traverses this rejection.

As indicated above, the claims have been amended to include structural features of the claimed recombinant inhibitor proteins that improve the affinity of said protein to a kallikrein.

Claims 39 and 40 have been amended to specify a recombinant inhibitor protein, or an inhibiting fragment thereof, which inhibits a kallikrein (*e.g.*, hK2), comprising a serpin sequence comprising a modified Reactive Serpin Loop (RSL) *having a substituted P1-P1'scissile bond-containing pentapeptide, which results in increased binding affinity for said kallikrein*. Claim 39 further requires that *P1 is an arginine (R) or a lysine (K).* Claim 41 has been amended to specify that the recombinant inhibitor protein, or inhibiting fragment thereof, comprise c*ertain SEQ ID NOs corresponding to the modified RSLs* described in the specification as having high affinity for kallikrein. Claim 43 has been amended to describe a recombinant inhibitor protein, or an inhibiting fragment thereof, which inhibits a kallikrein, comprising a serpin sequence comprising *a modified Reactive Serpin Loop (RSL), wherein P6 – P6' of the RSL comprises an arginine (R) or a lysine (K) at P1 and at least one additional substrate active site sequence*.

The Examiner suggests that claims 6, 9, 10, 17, 28-34, 36, 38-43, and 46 are not enabled because it would require undue experimentation to arrive at the recombinant inhibitor proteins. The Examiner alleges that the specification fails to establish regions within the claimed proteins which may be modified while improving kallikrein binding, and that the specification also fails to describe a "predictable scheme" for modifying substrate active site sequences. Applicant respectfully disagrees.

While Applicant asserts that the claims as originally written were fully enabled under the requirements set forth in 35 USC 112, first paragraph, Applicant submits that claims 6, 9, 10, 17, 28-34, 36, 38-43, and 46 have been amended to require structural features identified by Applicant as imparting improved kallikrein specificity. It is known in the art, and the specification teaches, that serpin proteins have an active site called an RSL which is highly conserved in structure and plays a role in the binding of target proteinases (see page 2 line 25 to page 3, line 20). The specification also teaches the importance of the P1-P1' bond of the RSL, as the specificity of serpins may be attributed to the residues at positions P1-P1' (see page 2, lines 25-32). Applicant provides working examples which describe kallikrein substrates

identified using phage display, which may be used in the RSL of a serpin to improve specificity of the serpin for a kallikrein, *e.g.*, hK2. The specification provides numerous examples of such pentapeptide sequences, including, for example, Tables I and IV. Tables I and IV both show that an arginine or a lysine at P1 of the RSL is important for increasing the binding affinity of the recombinant inhibitor protein for a kallikrein. The examples from Tables I and IV also describe the regions within the RSL which may be substituted by a pentapeptide specific for kallikrein, *e.g.*, P5 to P'4, P3 to P2', and P4 to P'1. Applicant also provides a working example of six recombinant inhibitor proteins comprising different modified RSLs that have improved binding affinity for kallikrein. Thus, the specification provides numerous examples of modified RSLs which may be used to arrive at the claimed invention.

In addition to the examples provided in the specification, Applicant also teaches how to identify other modified RSLs which may be used and how to make recombinant inhibitor proteins comprising a serpin and a modified RSL. As described above, the specification teaches at pages 22-23, that that peptides having improved specificity for kallikrein may be identified using a number of techniques, including combinatorial chemical libraries, immobilized peptide libraries, and phage display technology. Applicant also provides a working example of phage display technology in Example 1 at page 28, where six pentapeptides were identified and corresponded to changes in the RSL at positions P3-P3' (also described in Table IV). Applicant also teaches multiple other serpins which may be used in the proteins of the invention, including, for example, the serpins described in Table II. Thus, the specification not only teaches the important features of the RSL which may be modified to improve binding affinity for a kallikrein, it also provides describes how to make recombinant inhibitor proteins which incorporate these feature.

With respect to the Ngo *et al.* reference cited by the Examiner as teaching unpredictability in view of Applicant's invention, more specifically that there is a lack of correlation between protein sequences and activity, Applicant notes that the reference is dated 1994, ten years prior to the priority date of the instant application. Thus, Ngo *et al.* is not representative of the state of the art at the time of filing. Furthermore, Ngo *et al.* relates to computational prediction of protein structure based on linear protein sequences, and does not relate to predicting protein function based on structure as suggested by the Examiner. At page 491, the authors of the cited reference state that "it should be possible to write down a mathematical problem that, when solved, gives the native conformation of the protein." As

such, Applicant respectfully submits that Ngo *et al.* addresses a topic which is not presented by the instant invention, *i.e.*, protein structure prediction based on linear protein sequence.

Based on the teachings in the specification and the knowledge in the art at the time of filing, Applicant submits that one of ordinary skill in the art would not have to perform undue experimentation to arrive at the invention described in claims 6, 9, 10, 17, 28-34, 36, 38-43, and 46. Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 6, 9, 10, 17, 28-34, 36, 38-43, and 46 for lack of enablement.

Rejection of claims 9, 17, 28, 30, 32, 33, 36, 38-40, 42, 43, and 46 under 35 U.S.C. § 102(b)

The Examiner has rejected claims 9, 17, 28, 30, 32, 33, 36, 38-40, 42, 43, and 46 under 35 U.S.C. § 102(b) for lack of novelty. The Examiner suggests that claims 9, 17, 28, 30, 32, 33, 36, 38-40, 42, 43, and 46 are anticipated by Schechter *et al.* (*J Biol Chem*, (1993) 268(31):23626) in view of evidentiary reference Rubin *et al.* (*J Biol Chem*. (1990) 265(2):1199). Applicant respectfully traverses this rejection.

As described above, amended claims 9, 17, 28, 30, 32, 33, 36, 38-40, 42, 43, and 46 are directed to recombinant inhibitor proteins comprising a serpin sequence comprising a modified RSL, wherein the RSL comprises a *pentapeptide which increases binding of the recombinant inhibitor protein to a kallikrein*, *e.g.*, hK2. More specifically, amended claims 39 and 40 require that the recombinant inhibitor proteins comprise a *modified RSL having a substituted P1-P1' scissile bond-containing pentapeptide, which results in increased binding affinity for a kallikrein or hK2*, respectively. Amended claim 43 is directed to a recombinant inhibitor protein comprising a serpin sequence comprising a modified Reactive Serpin Loop (RSL) *comprising a pentapeptide*, wherein P1of the RSL is an arginine (R) or a lysine (K) and P6 – P6' of the RSL is modified by at least one additional substrate active site sequence.

Applicant submits that the Schechter reference cited by the Examiner does not teach each and every element of claims 9, 17, 28, 30, 32, 33, 36, 38-40, 42, 43, and 46, as required under 35 U.S.C. § 102(b). Schechter *et al.* describe single mutations within the ACT protein, as well as a hexamer substitution at P3-P3', to determine the impact of said mutations on ACT's ability to inhibit chymase.

Applicant's invention is based on pentapeptides which are included in the RSL of recombinant inhibitor proteins and impart advantageous binding properties to the recombinant inhibitor protein *such that the protein has improved binding affinity for kallikrein*. There is no

teaching or suggestion in Schechter *et al.* that the recombinant proteins described therein would have an increased affinity for kallikrein, as kallikrein is quite distinct from chymase described in the cited reference. The Schechter reference also does not teach recombinant inhibitor proteins comprising pentapeptides within the RSL, as required by independent claims 39, 40, and 43. Thus, Schechter *et al.* does not teach all of the elements of the claimed invention, and, as such, does not anticipate amended claims 9, 17, 28, 30, 32, 33, 36, 38-40, 42, 43, and 46. Applicant respectfully requests that the Examiner withdraw the rejection of claims 9, 17, 28, 30, 32, 33, 36, 38-40, 42, 43, and 46 under 35 U.S.C. § 102(b).

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. KZI-003US.

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Respectfully submitted,

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